R E M A R K S

The Office Action of August 16, 2002 presents the examination of claims 34, 41, 42, and 48-52. Claim 34 is allowed. Claims 41, 42, and 48-52 remain rejected.

Claims 41 and 51 are amended. Applicants amend claim 41 to change the position of the phrase "a complement of", to be identical to that of claim 42. Applicants amend claim 51 to replace GenBank accession numbers with appropriate SEQ ID NOs, as discussed below.

New claims 56-61 are added. Claims 56 and 57 are identical to claims 41 and 42, respectively, except that they recite the phrase "80% homology." Support for "80% homology" is found on page 20, lines 23-25 of the specification. Claims 58 and 59 are directed to SEQ ID NOs: 5 and 10, which were cloned by hybridization using SEQ ID NOs: 1 or 2 as a probe (see, Example 4 of the specification). Finally, claims 60 and 61 are identical to claims 41 and 42, respectively, except that they recite the phrase "90% homology." Support for "90% homology" is also found on page 20, lines 23-25 of the specification.

For these reasons, no new matter is inserted into the application.

Substitute Sequence Listing

Enclosed herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a substitute Sequence Listing to be inserted into the specification as indicated above. The substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a disk copy of the substitute Sequence Listing. The disk copy of the substitute Sequence Listing, file "2003-02-19 0020-4546P seq list.txt", is identical to the paper copy, except that it lacks formatting.

Interview

An interview with the Examiner was conducted on January 13, 2003. The assistance of the Examiner in advancing prosecution of the present application is much appreciated.

Claim Objections

The Examiner states that the incorporation of essential material into claim 51 by reference to GenBank Accession numbers is improper. The Examiner states that the specification must be amended to include the incorporated material, and a declaration

must be filed stating that the amendatory material consists of the same material incorporated by reference in the referencing application at the time of filing.

In response to the Examiner's remarks, Applicants submit a substitute Sequence Listing that includes the GenBank sequences. Applicants will consider filing a Declaration in the near future. GenBank Accession No: R54387 was created on May 18, 1995, and the 517 nucleotide-long sequence presented therein is the sequence disclosed in the present application as SEQ ID NO: 15 in the substitute Sequence Listing enclosed herewith. See, Exhibit 12 filed with the Reply under 37 C.F.R. § 1.111 filed on November 20, 2001. GenBank Accession No: T09073 was created on May 25, 1993 and last updated on August 3, 1993, and corresponds to SEQ ID NO: 16 of the substitute Sequence Listing enclosed herewith. A copy of GenBank Accession No: T09073 obtained from NCBI Sequence Viewer is attached hereto.

During the interview held on January 13, 2003, the Examiner was informed that Applicants would overcome the rejection of claims 51 and 52 by amending the specification and providing a declaration. The Examiner stated that this course of action was

acceptable. For these reasons, Applicants respectfully submit that the objection of claim 51 is overcome.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 51 and 52 for allegedly being indefinite under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner asserts that the phrase "at least 27 contiguous nucleotides disclosed in GenBank Accession No: T09073 or GenBank Accession No: R54387" is vague since the disclosure of the sequences in GenBank may change (i.e., be amended) with time.

In order to answer this rejection, Applicants amend the GenBank Accession numbers to SEQ ID NOs as noted above. Thus, the instant rejection is overcome.

Rejection under 35 U.S.C. § 112, first paragraph

Written Description

Claims 41, 42 and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description of the invention. Applicants respectfully traverse. Reconsideration of

the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that the washing conditions recited in claims 41 and 42 (i.e., 2xSSPE and 42°C) are of low stringency, and as such, the claims encompass sequences having low homology to SEQ ID NOs: 1 and 2. Specifically, the Examiner states, "The claimed nucleic acid could vary dramatically from the disclosed nucleotide sequences of the present application." See, page 5, lines 7-8 of the Office Action.

Applicants respectfully submit that the Examiner's assertions are not pertinent. First, Applicants point out that the hybridization conditions recited in claims 41 and 42 are equivalent to, or even more stringent than, the hybridization conditions described in Example 9 of the USPTO "Revised Interim Written Description Guidelines Training Materials." Example 9 of the Training Materials addresses claims that recite the invention is terms of hybridization to a reference sequence. Thus, Example 9 is relevant to the instant claims 41 and 42. The claim in Example 9 states:

> An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the

complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

Thus, Example 9 only provides hybridization conditions (6xSSC, 65°C), a reference sequence, and protein function. This claim language is identical in its general content that that of the instant claims 41 and 42. The hybridization conditions set forth in the instant claims are considered to be highly stringent in the art as shown by Exhibit 5 (submitted in the Reply filed on November 20, 2001)[1]. A reference sequence is set forth in claims 41 and 42, as well as the biological activity of the protein. Furthermore, the instant specification contains a similar description as Example 9 (see, Examples 1, 3, 4, and 7-9 of the specification). During the interview, the Examiner maintained that the washing conditions are of too low stringency. Applicants respectfully point out that

[1] The conditions recited in the claims are equivalent to hybridization at 65°C in an aqueous buffer, indeed they provide a higher stringency. Note that in the equation on page 9.51 of Exhibit 5, the inclusion of 45% formamide lowers the Tm by 28°C. Thus, the buffer conditions recited in the instant claims provide stringency equivalent to hybridization in aqueous solution at a temperature of about 37°C, and the use of 42°C as the hybridization temperature provides even greater stringency.

Example 9 does not even recite washing conditions. Thus, the Examiner improperly relies on an element missing from Example 9 of the Training Materials to maintain the rejection. Accordingly, claims 41 and 42 meet the requirements of 35 U.S.C. § 112, first paragraph, written description.

Second, a search conducted by Applicants also demonstrates that claims 41 and 42 meet the requirements of written description. Applicants conducted a search for a gene which can hybridize to SEQ ID NO: 2 under the conditions as defined in claims 41 and 42, and has 80% or more sequence identity with SEQ ID NO: 2 using existing databases (GenBank, EMBL, DDBJ, and PDB). The search results are presented in a Declaration under 37 C.F.R. § 1.132 executed by Dr. KIKUCHI, attached hereto.

As specifically shown in the Declaration, about 1,600,000 kinds of sequences available from the existing databases were searched using BLASTN (default). It is known in the art that nucleotide sequences hit in the search for a homologue of a given DNA using said software BLASTN have 80% or more identity to said DNA in question. The sequences hit were evaluated regarding the relevance to Semaphorin W according to the Alignment score, Bit score, and E-value.

As shown in Figure 1 attached to the Declaration, 58 kinds of sequences hit (one sequence corresponds to one line), which should have at least 80% homology to SEQ ID NO:2. Among the 58 sequences, those relevant to Semaphorin W (depicted by pink or red lines) according to the Alignment score, Bit score, and E-value are identical to Semaphorin W over a wide range. On the other hand, DNAs irrelevant to Semaphorin W (depicted by green or blue lines), show homology to only a small partial region (less than 30 base pairs) of Semaphorin W. Thus, the computer search reveals that DNAs having 80% or greater homology to SEQ ID NO:2 over a wide range of Semaphorin W are all related to Semaphorin W.

The search result demonstrates that, contrary to the Examiner's assertions, the claimed nucleic acids do not vary dramatically from the disclosed nucleotide sequences of the present application. Turning to claims 41 and 42, the sequences irrelevant to Semaphorin W are excluded from the scope of the claims, since they cannot hybridize to the entire sequence of SEQ ID NOs: 1 or 2, nor show the biological activity recited in the claims. Thus, claims 41 and 42 encompass appropriately only nucleic acids falling within the scope of the invention.

For all the above reasons, Applicants respectfully submit that the instant claims fully comply with 35 U.S.C. § 112, first paragraph, written description. Accordingly, withdrawal of the instant rejection is therefore respectfully requested.

Enablement

Claims 41, 42 and 48-50 are rejected under 35 U.S.C. § 112, first paragraph for allegedly not being enabled by the specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

During the interview, the Examiner emphasized that a sequence with 80% homology to SEQ ID NO:1 or 2 could have up to 200 modifications. The Examiner stated that the specification does not enable this amount of possible modifications. In other words, the Examiner asserts that one of ordinary skill in the art cannot predict *a priori* if any particular variation of the nucleotide sequences will encode a protein having the biological activities stated in the claims.

Applicants respectfully submit that the Examiner improperly relies solely on unpredictability in maintaining the enablement

rejection. The Skolnick reference cited in the Office Action merely evidences inability to predict protein function from protein structure. Its citation only underscores the Examiner's improper reliance upon only one of the factors (i.e. unpredictability) that must be weighed in considering enablement. Applicants have previously presented their view of the so-called "Wands" factors to be considered in determining enablement. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). The Examiner does not provide any substantial rebuttal of these arguments, but instead merely states in a conclusory manner that unpredictability of biological function of a protein would cause one skilled in the art undue experimentation to practice the full scope of the invention as claimed.

Applicants again assert that one of ordinary skill in the art can readily utilize the cloned DNAs deposited by the Inventors as starting materials to perform mutation and screening experiments by methods known in the art and described in detail in the specification. Further, as explicitly held in the *Wands* case, this type of mutation-screening approach to identify additional embodiments of the invention is not undue experimentation. Thus, even if the possible amount of experimentation needed to create the

possible modifications to SEQ ID NOs: 1 and 2 is large, the experimentation itself is routine in the art and not undue.

During the interview, the Examiner stated further evidence (such as in the form of journal articles) showing that the semaphorin domain is known in the art, and that one of skill in the art would know not to modify this region, might be persuasive in overcoming the enablement rejection. In response to the Examiner's remarks, Applicants submit herewith A. Kolodkin et al., *Cell*, 75 (1993) 1389-1399. This journal article shows that the Semaphorin domain is known in the art. Although said journal article may not directly show that one of skill in the art would know not to modify the Semaphorin domain, it clearly shows that the Semaphorin domain comprises many well conserved residues that are known in the art not the be modified. In Figure 2 on page 1390 of the article, the Semaphorin domain is indicated by two arrows ↓ and ↑, and in Figure 3 on page 1391, the Semaphorin domain is shown as the shaded portions. From Figures 2 and 3, one of ordinary skill in the art can easily understand that the Semaphorin domain comprises many well-conserved residue(s), such as cysteine, which should not be modified.

For all the above reasons, Applicants respectfully submit that the instant claims fully comply with 35 U.S.C. § 112, first paragraph, enablement. Accordingly, withdrawal of the instant rejection is therefore respectfully requested.

Conclusion

Applicants respectfully submit that all of the outstanding issues precluding allowance of the present application have been addressed and overcome by Applicants, such that the instant claims are now in condition for allowance. The favorable action of allowance of all of the pending claims is respectfully requested.

Attached hereto is a marked-up version of the changes made to the application by this Reply.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at (703) 205-8000.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of three (3) months to February 16, 2003, in which to file a reply to the Office Action. The required fee of $930.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,
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0020-4546P

Attachments: Version with Markings to Show Changes Made;
GenBank Accession No: T09073;
Declaration under 37 C.F.R. § 1.132 executed by Dr. KIKUCHI;
A. Kolodkin et al., *Cell*, 75 (1993) 1389-1399;
Substitute Sequence Listing and Disk

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 56-61 are added.

Claims 41 and 51 are amended as follows:

Claim 41. (Four Times Amended) An isolated nucleic acid molecule comprising [a complement of] a polynucleotide that specifically hybridizes with a complement of a polynucleotide having a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1; and

(b) the nucleotide sequence of SEQ ID NO:2;

under conditions of a buffer comprising 45%(v/v) formamide, 5x SSPE, at 42°C, and washing after hybridization with a buffer comprising 2xSSPE at 42°C, and that encodes a protein having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion cells.

Claim 51. (Four Times Amended) An isolated nucleic acid molecule consisting of a single-stranded polynucleotide consisting of at least 27 contiguous nucleotides of SEQ ID NO:2, 4, or 10 with the proviso that said nucleic acid molecule does not consist of a

polynucleotide consisting of at least 27 contiguous nucleotides disclosed in SEQ ID NO:16 [GenBank Accession No:T09073] or SEQ ID NO:15 [GenBank Accession No:R54387].